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EDITORIAL COMMENT

# Block the Ischemia and Reperfusion Damage

## An Old Adjunctive Drug for a New Reperfusion Strategy*

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When the short-term primary endpoint of a randomized study is met, generally, the long-term secondary endpoint analysis is less relevant, and not infrequently, the acute benefit of a treatment is diluted or not maintained over time. This is not the case for the METOCARD-CNIC (Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial (1,2). In this issue of the *Journal*, Ibanez et al. (2) report the long-term results of a primary percutaneous coronary intervention (PCI) randomized trial that assessed the impact on infarct size of intravenous

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metoprolol administration before mechanical intervention in patients with acute anterior myocardial infarction. The primary endpoint of the study was infarct size as assessed by magnetic resonance imaging (MRI) at 1 week after intervention. The primary endpoint of the study was met: patients randomized to metoprolol had smaller infarcts than control subjects (25.6 ± 15.3 g vs. 32.0 ± 22.2 g; adjusted difference −6.52; 95% confidence interval [CI]: −11.39 to −1.78; p = 0.012), and this effect was evident just in patients with an occluded infarct artery before intervention (26.7 ± 15.0 g in metoprolol patients vs. 34.4 ± 20.0 g in the control group, adjusted difference −8.13; 95% CI: −13.10 to −3.16; p = 0.0024), whereas no significant effect was revealed in patients with an already open infarct artery at baseline angiography (20.7 ± 16.4 g in the metoprolol group vs. 22.2 ± 28.3 g in the control group, p = 0.6), confirming that pre-intervention metoprolol is effective in decreasing reperfusion myocardial damage (1). At 6 months, 202 patients (101 per group) of the 216 eligible patients (93%) had repeat MRI that showed a dramatic decrease in severe left ventricular remodeling and dysfunction in the metoprolol group: a left ventricular ejection fraction <35% was revealed in 11% of patients in the metoprolol group and 27% in the control group, p = 0.006 (2). Again, at 2-year follow-up, the rate of readmission for congestive heart failure was more than halved in the metoprolol group (2.2% vs. 6.9%; p = 0.046), as well as the number of patients who received cardioverter-defibrillator implantation (2). The survival curves of readmission for congestive heart failure continue to diverge after 1 year, confirming that the early benefit of pre-intervention metoprolol may increase over time according to the long process of left ventricular remodeling toward clinical heart failure.

Thus, despite the fact that the study was not powered for clinical endpoints, the results of the MRI and clinical follow-up suggest a strong impact of pre-reperfusion metoprolol on clinical outcome with obvious economic implications.

Several characteristics of the METOCARD-CNIC trial deserve specific comments in order to understand the strengths of the study. First, the inclusion criteria included only anterior myocardial infarctions without hemodynamic instability, allowing the recruitment of large myocardial infarctions without safety issues as a result of the negative inotropic effect of metoprolol. Second, this is mechanistic trial that included in the protocol a paired MRI to assess the effects of infarct size on left ventricular remodeling over time, and the MRI follow-up rate was very high, making the demonstration of the link between infarct size and left ventricular remodeling unquestionable. Third, the effects of pre-intervention metoprolol on infarct size, left ventricular remodeling, and readmission for congestive heart failure were evident despite the fact that approximately 20% of patients who received the drug had an already open infarct artery at the time of intervention, rendering the drug ineffective in terms of prevention of reperfusion damage. Finally, the rates of all components of the composite clinical endpoint of death from any cause, malignant ventricular arrhythmias, reinfarction, and admission for congestive heart failure were better in the metoprolol arm, with a resulting strong trend favoring metoprolol (endpoint rate 10.8% in the metoprolol arm and 18.3% in the control arm, p = 0.065). The clinical implications of this result are important despite the p value, when considering the small number of patients, the inclusion in the endpoint of patients who died from noncardiac causes that were not related to the study treatment, and the high likelihood of a progressive increase in adverse events in the control arm during a longer follow-up.

It is surprising that the METOCARD-CNIC trial is the first randomized study on adjunctive beta-blocker treatment before mechanical intervention, considering that a strong benefit of pre-reperfusion beta-blocker treatment was already suggested many years ago in retrospective analyses from the PAMI (Primary Angioplasty in Acute Myocardial

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Infarction) and the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials (3,4). In these post-hoc analyses, patients who received a beta-blocker before PCI had a strong benefit in short-term survival as compared with patients who did not receive the drug. In the CADILLAC patient cohort, the benefit was entirely limited to patients who did not receive the drug before admission, and the multivariable analysis showed pre-intervention beta-blocker treatment independently related with 30-day mortality (hazard ratio: 0.38, 95% CI: 0.17 to 0.87, $p = 0.02$) (4). From those years, a plethora of studies with drugs or devices were conducted to reduce reperfusion myocardial damage. Most of these studies, including large empirical pharmacology trials or smaller mechanistic device trials, failed to demonstrate any benefit. Also, studies using complex and expensive techniques, such as cooling and hyperoxemic reperfusion, have not provided convincing results. Thus, until now, restoring a full (microvascular) reperfusion while avoiding reperfusion damage has remained elusive in many patients despite the evidence of cardioprotection exerted by many agents and techniques in animal models.

The results of the trial are particularly appealing because they show that an effective cardioprotection can be achieved with intravenous metoprolol before reperfusion at a very low price and with ease of administration. These characteristics make highly feasible a clinical trial powered for long-term clinical endpoints such as cardiac mortality and congestive heart failure that will provide a definite answer to the routine use of beta-blockers before mechanical myocardial reperfusion in acute myocardial infarction.

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